Priority data gaps for quantifying the impact of novel syphilis interventions: A mathematical modeling analysis

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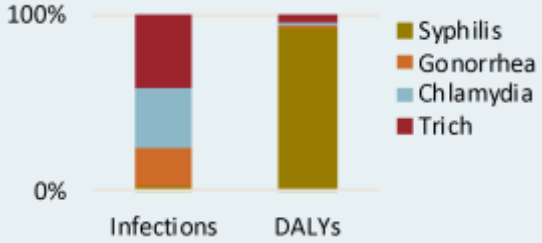
What we do and don't know about syphilis

The burden of syphilis is both substantial and increasing

- >1M new STIs are acquired every day[1]
- Syphilis makes up a small share of infections, but >85% of STI-attributable DALYs[2]

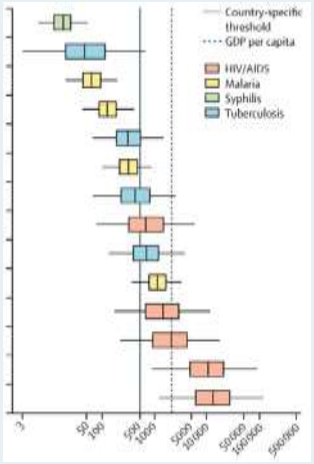


- Syphilis is estimated to account for ~8% of preventable stillbirths[3] (malaria: 8%, NCDs: 7%)
- Syphilis is trending sharply higher, esp in HICs[4-6]
- Majority of DALYs are in LMICs, esp in Sub-Saharan Africa

US: 80% (2018-22)
UK: 29% (2022-23)
Canada: 389% (2011-19)

We understand the basics of how syphilis progresses and how to treat it

- Preventable and curable
- Treated with benzathine penicillin (BPG) injection
- Treatment is very effective, including during pregnancy[7]

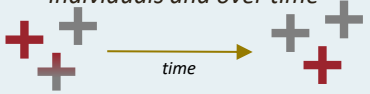


Infection with *T pallidum*
10-90 days
Primary syphilis: genital ulcers
~1 month
Secondary syphilis: rash
~3 months
Early latent syphilis: asymptomatic
1-2 years
Late latent syphilis: asymptomatic
Decades
Tertiary syphilis: systemic

But we don't know how it transmits by stage, or the true scale of the burden

- People are known to be highly infectious during primary & secondary stages of infection, when symptoms are present
- **How long do people remain transmissible for?**
- Recent studies have found T pallidum at mucosal sites of people with latent infection
- Our understanding of transmission could change dramatically depending on what this looks like

Transmissibility may vary across individuals and over time



Abbreviations: STI: sexually transmitted infection; DALYs: disability-adjusted life years; NCDs: non-communicable diseases; HIC: high-income country; LMIC: low-middle income country; BPG: benzathine penicillin

1. WHO Global Health Observatory, 2020 | 2. IHME's Global Health Data Exchange Results Tool for GBD 2021 | 3. Lawn et al 2016, *Lancet*| 4. US CDC 2022 surveillance report | 5. UK Health Security Agency press release 2023 | 6. Public Health Agency of Canada press release 2023 | 7. Silke F et al. Lancet Global Health 2024

Using mathematical modeling, we can quantify the value of information to understand what data would help us most

Clear case for improved syphilis control, but value depends on unknown factors

1. **What are the use cases for novel point-of-care diagnostics?**
2. When & how often should pregnant women be screened for syphilis?
3. What's the potential benefit of a syphilis vaccine?

Better data helps quantify value, but which data are most important?

1. **Better estimates of transmission dynamics?**
2. Better estimates of syphilis burden?
3. Better estimates of syphilis sequalae and DALYs?

Better modeling can help prioritize and focus data collection

Example of a **less important** missing input	Assume low value	Low ICER	Fund vaccine development
	Assume high value	Low ICER	Fund vaccine development
Example of a **very important** missing input	Assume low value	High ICER	Don't fund vaccine development
	Assume high value	Low ICER	Fund vaccine development

Aims of this work

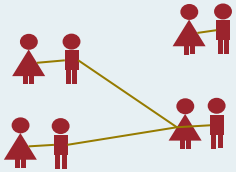
1. **Objective:** Estimate the value of improved data on syphilis transmission dynamics	– Inform data collection prioritization – Improve delivery strategies
2. **Study design**: simulation study using an agent-based model of HIV and syphilis	– Leverage richness of HIV data – Capture correlations
3. **Setting**: Zimbabwe	– Data-rich setting, strong collaborators

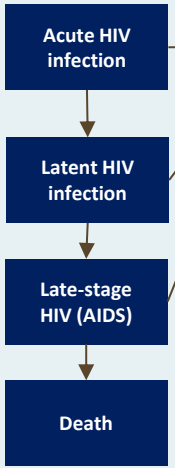
Abbreviations: DALYs: disability-adjusted life years; ICER: incremental cost-effectiveness ratio

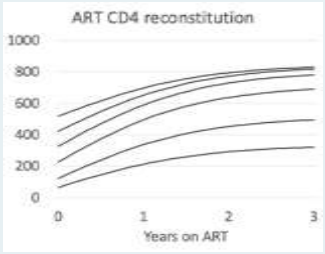
Transmission model approach and overview

Model structure

- **Agent-based model** with a risk- and age-stratified sexual network
- Simplified HIV model







Model implementation & calibration

- Implemented in the Starsim software

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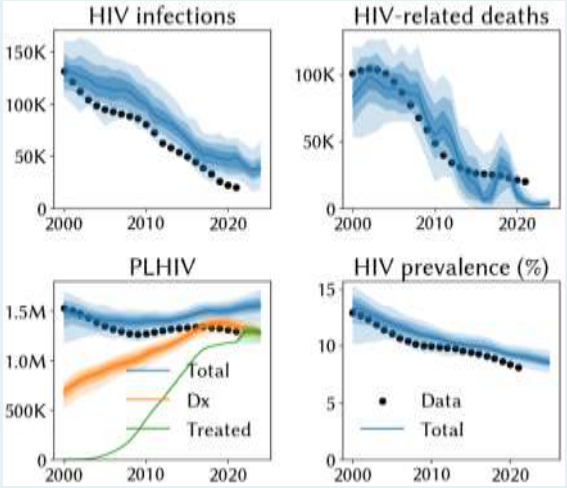
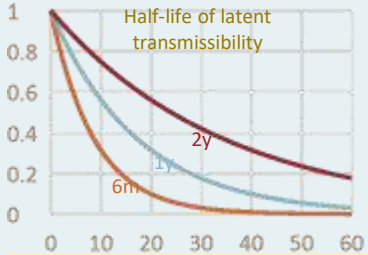
- Calibrate HIV transmission and sexual behavior parameters to fit HIV data and behavioral data from DHS & ZIMPHIA



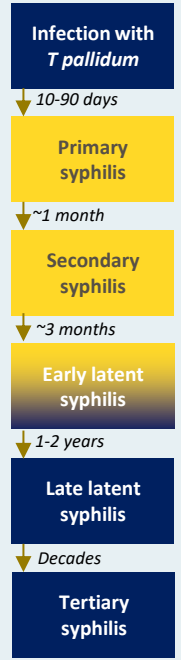
Model analysis

- Add a syphilis module, varying the rate of decay of transmissibility post-latency
- Longer infectiousness => lower transmission probability



KEY ANALYSIS QUESTIONS

1. How would transmission patterns change?
2. Would the the impact of new diagnostics for active syphilis change?

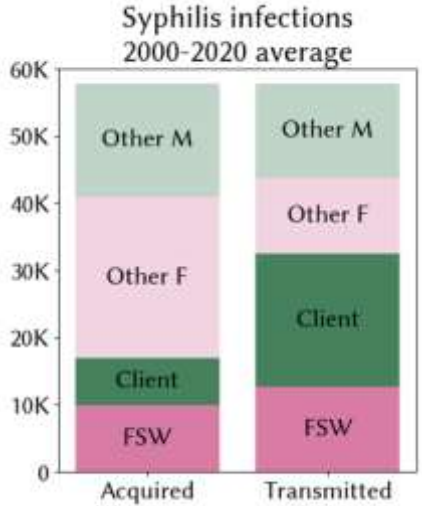


Abbreviations: ZIMPHIA: Zimbabwe; ART: antiretroviral treatment; PLHIV: people living with HIV; Dx: diagnosed: POC: point-of-care

Result 1: rapidly-declining latent transmission implies that key populations and young people drive more transmission

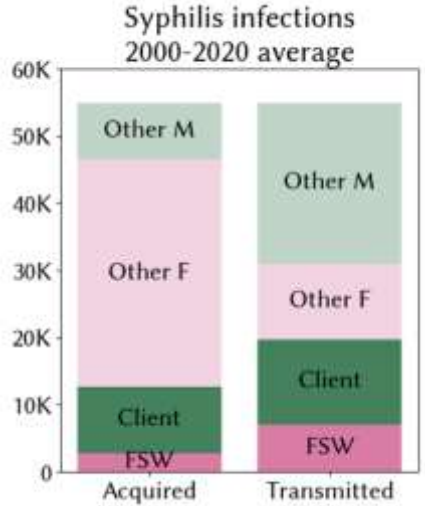
Scenario 1: half-life of latent transmissibility = 1 year

- **56%** of infections directly attributable to sex work
- **25%** of infections in 20-25yo



Scenario 2: half-life of latent transmissibility = 2 years

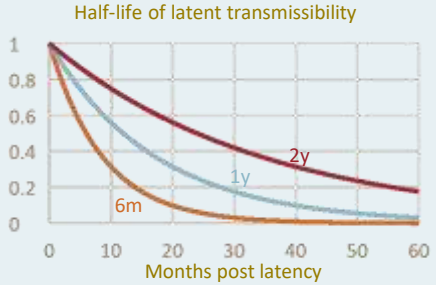
- **36%** of infections directly attributable to sex work
- **18%** of infections in 20-25yo



Interpretation

Across scenarios varying half-life of latent transmission from 0.5-2y:

- With a **shorter** duration of latent infection (6m half-life), more transmission is driven by **sex work** and **young women**
- With a **longer** duration of latent infection (2y half-life), **transmission is less concentrated**



Half-life	Sex work %	F 20-25 %
6m	80%	31%
1y	56%	25%
2y	36%	18%

Implications for optimal delivery strategies for interventions?

Abbreviations: FSW: female sex workers

Result 2: better diagnosis of primary syphilis is most effective at interrupting transmission if that's where transmission occurs

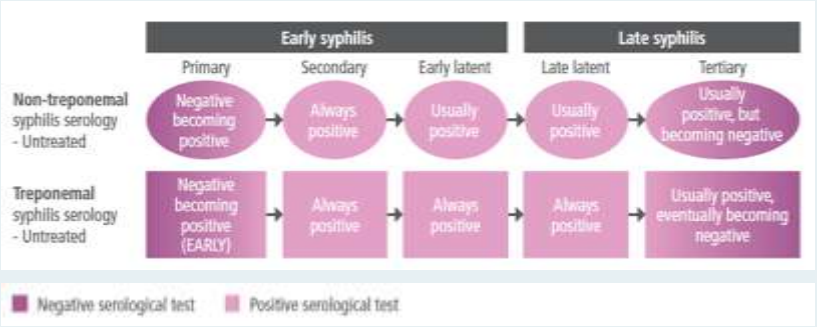
There is a need for point-of-care (POC) syphilis diagnostics

Syphilis diagnosis requires:

- Detection of Treponemal spirochetes OR
- Positive result in two unrelated serological assays

Three major diagnostic gaps:

1. Diagnosing genital ulcer disease (GUD): serology has a window period
2. Diagnosing congenital syphilis in newborns as serology may be false-positive due to maternal antibodies
3. Diagnosing individuals previously treated for syphilis as antibodies persist lifelong



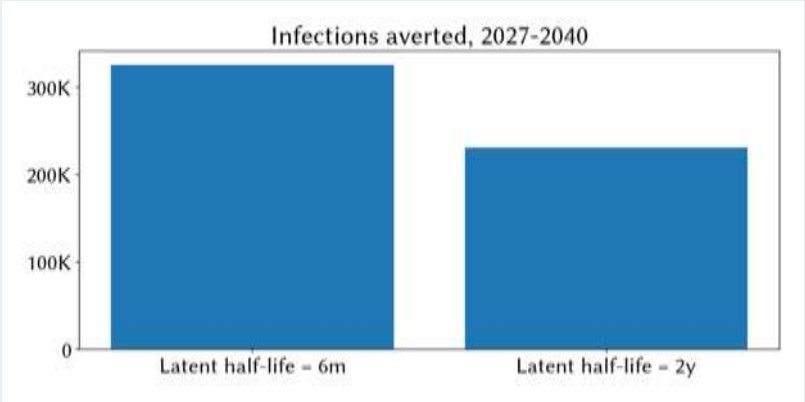
Value is highest if transmission occurs most in primary phase

Latent transmission scenarios

Half-life	Sex work %	F 20-25 %
6m	80%	31%
2y	36%	18%

Diagnostic scenarios

	Syndromic management[1]	Etiological GUD panel
Sensitivity	20%	95%
Specificity	92.6%	95%



Abbreviations: GUD: genital ulcer disease

1. WHO Guidelines for the management of symptomatic sexually transmitted infections (2021)

Conclusions & acknowledgments

Conclusions

- Syphilis is an old disease, but much remains poorly understood
- We used an HIV-syphilis coinfection model calibrated to data from Zimbabwe to show how very different epidemiological pictures emerge depending on the extent of latent transmission of syphilis

Shorter duration of infectiousness
- **Larger** role of key populations
- **More impact** of GUD diagnostics

Longer duration of infectiousness
- **More generalized** transmission
- Lesser impact of GUD diagnosis

Focusing data collection on understanding the extent of latent transmission of syphilis would highlight the optimal use cases for novel diagnostics + best delivery strategies

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- Marcus Chen (Monash U)

References

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Related talks

★ *THURSDAY: STARSIM LEARNING DAY* ★
- Starsim lunch & learn, 12.45-1.15pm today
- Vaccine-preventable disease, 1.30pm today
- Poster session, 5pm today
- Agent-based modeling showcase, 10.15 Wed
- Modeling methods, 1.30pm Wed

Thank you!